This label may not be the latest approved by FDA.
urrent labeling information, please visit https://www.fda.gov/drugs

Each tablet contains:
Nevirapine, USP (anhydrous) 100 mg

Usual Dosage: See accompanying prescribing information.

Tablets must be swallowed whole and must not be chewed, crushed, or divided.

Keep this and all medication out of the reach of children.

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

Manufactured for:
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.
Made in India

RMXA6950H

Mylan® | Mylan.com

NDC 0378-6950-93

Nevirapine Extended-release Tablets

100 mg

PHARMACIST: Dispense the accompanying Medication Guide to each patient.

Mylan®

Rx only **30 Tablets**

N 3 0378-6950-93 5

75056689

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

Keep container tightly closed.

Code No.: MH/DRUGS/AD/089

VARNISH FREE AREA

Prompt "LOT" & "EXP" will be printed together with Variable Data Coading.

This label may not be the latest approved by FDA.
urrent labeling information, please visit https://www.fda.gov/drugs

Each tablet contains:
Nevirapine, USP (anhydrous) 100 mg

Usual Dosage: See accompanying prescribing information.

Tablets must be swallowed whole and must not be chewed, crushed, or divided.

Keep this and all medication out of the reach of children.

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

Manufactured for:
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.
Made in India

RMXA6950MM

Mylan® | Mylan.com

NDC 0378-6950-77

Nevirapine Extended-release Tablets

100 mg

PHARMACIST: Dispense the accompanying Medication Guide to each patient.

Mylan®

Rx only **90 Tablets**

N 3 0378-6950-77 5

75056348

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.
Keep container tightly closed.
Code No.: MH/DRUGS/AD/089

VARNISH FREE AREA

Prompt "LOT" & "EXP" will be printed together with Variable Data Coading.

This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

Each tablet contains:
Nevirapine, USP (anhydrous) 100 mg

Usual Dosage: See accompanying prescribing information.

Tablets must be swallowed whole and must not be chewed, crushed, or divided.

Keep this and all medication out of the reach of children.

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

This container is not intended for dispensing for household use.

Manufactured for:
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

Made in India

RMXA6950B

Mylan® | Mylan.com

NDC 0378-6950-05

Nevirapine Extended-release Tablets

100 mg

PHARMACIST: Dispense the Medication Guide provided separately to each patient.

Mylan®

Rx only **500 Tablets**

N 3 0378-6950-05 8

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.
Keep container tightly closed.
Code No.: MH/DRUGS/AD/089

VARNISH FREE AREA

Prompt "LOT" & "EXP" will be printed together with Variable Data Coading.

75056730

This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

NEVIRAPINE EXTENDED-RELEASE TABLETS 100 mg
MXA:NEV1:R1mmh 75056349

NEVIRAPINE EXTENDED-RELEASE TABLETS 100 mg
MXA:NEV1:R1mmh 75056349

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use nevirapine extended-release tablets safely and effectively. See full prescribing information for nevirapine extended-release tablets.

NEVIRAPINE extended-release tablets, for oral use
Initial U.S. Approval: 1996

WARNING: LIFE-THREATENING (INCLUDING FATAL) HEPATOTOXICITY and SKIN REACTIONS
See full prescribing information for complete boxed warning.

- **Fatal and non-fatal hepatotoxicity (5.1)**
- **Fatal and non-fatal skin reactions (5.2)**

Discontinue immediately if experiencing:

- **Signs or symptoms of hepatitis (5.1)**
- **Increased transaminases combined with rash or other systemic symptoms (5.1)**
- **Severe skin or hypersensitivity reactions (5.2)**
- **Any rash with systemic symptoms (5.2)**

Monitoring during the first 18 weeks of therapy is essential. Extra vigilance is warranted during the first 6 weeks of therapy, which is the period of greatest risk of these events. (5)

---------- INDICATIONS AND USAGE ----------

- Nevirapine extended-release tablets are an NNR I indicated or combination antiretroviral treatment o HIV-1 in ection in adults and in children 6 to less than 18 years o age. (1)

Important Considerations:

- Initiation o treatment is not recommended in the ollowing populations unless the bene its outweigh the risks. (1, 5.1)
  - o adult emales with CD4 cell counts greater than 250 cells/mm^3
  - o adult males with CD4 cell counts greater than 400 cells/mm^3
- he 14-day lead-in period with immediate-release nevirapine (200 mg once daily) must be strictly ollowed; it has been demonstrated to reduce the requency o rash. (2.5, 5.2)

---------- DOSAGE AND ADMINISTRATION ----------

- he nevirapine extended-release tablets must be swallowed whole and must not be chewed, crushed, or divided. (2.1)
- Adult patients must initiate therapy with one 200 mg tablet o immediate-release nevirapine once daily or the irst 14 days, ollowed by one 400 mg tablet o nevirapine extended-release once daily. (2.2)
- Adult patients already on a regimen o immediate-release nevirapine twice daily can be switched to nevirapine extended-release tablets 400 mg once daily without the 14-day lead-in period o immediate-release nevirapine. (2.2)
- Pediatric patients (ages 6 to less than 18 years) must initiate therapy with immediate-release nevirapine (as 150 mg/m^2 o nevirapine oral suspension or as nevirapine tablet) at a dose not to exceed 200 mg per day administered once daily or the irst 14 days, ollowed by nevirapine extended-release tablets once daily as shown in the ollowing table. (2.3)

Recommended Dosing for Pediatric Patients 6 to less than 18 years of age by BSA after the Lead-in Period	
BSA range (m^2)	**Nevirapine Extended-release Tablets Dose (mg)**
0.58 to 0.83	200 mg once daily (2 x 100 mg)
0.84 to 1.16	300 mg once daily (3 x 100 mg)
Greater than or equal to 1.17	400 mg once daily (1 x 400 mg)

- Pediatric patients already on a regimen o twice-daily nevirapine oral suspension or immediate-release nevirapine tablets can be switched to nevirapine extended-release tablets once daily without the 14-day lead-in period o nevirapine oral suspension or immediate-release nevirapine tablets. (2.3)
- I any patient experiences rash during the 14-day lead-in period with immediate-release nevirapine do not initiate nevirapine extended-release tablets until the rash has resolved. Do not continue the immediate-release nevirapine lead-in dosing regimen beyond 28 days. (2.5)
- I dosing is interrupted or greater than 7 days, restart 14-day lead-in dosing. (2.5)

---------- DOSAGE FORMS AND STRENGTHS ----------

- 100 mg tablets (3)

---------- CONTRAINDICATIONS ----------

- Patients with moderate or severe (Child-Pugh Class B or C, respectively) hepatic impairment. (4.1, 5.1, 8.7)
- Use as part o occupational and non-occupational post-exposure prophylaxis (PEP) regimens, an unapproved use. (4.2, 5.1)

---------- WARNINGS AND PRECAUTIONS ----------

- Hepatotoxicity: Fatal and non- atal hepatotoxicity has been reported. Monitor liver unction tests be ore and during therapy. Permanently discontinue nevirapine i clinical hepatitis or transaminase elevations combined with rash or other systemic symptoms occur. Do not restart nevirapine a ter recovery. (5.1)
- Rash: Fatal and non- atal skin reactions, including Stevens- ohnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions, have been reported. Permanently discontinue nevirapine i severe skin reactions or hypersensitivity reactions occur. Check transaminase levels immediately or all patients who develop a rash in the irst 18 weeks o treatment. (5.2)
- Monitor patients or immune reconstitution syndrome and at redistribution. (5.5, 5.6)

---------- ADVERSE REACTIONS ----------

- Adult patients: he most common adverse reaction is rash. During the lead-in period with immediate-release nevirapine, the incidence o Grade 2 or higher drug-related rash in adults is 3%. A ter the lead-in period the incidence o Grade 2 or higher drug-related rash in subjects taking nevirapine extended-release tablets is 3%. he incidence o Grade 2 or higher drug-related clinical hepatitis a ter the lead-in phase was 2%. (6.1)
- Pediatric patients: he incidence o Grade 2 or higher drug-related rash was 1%. (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact Mylan Pharmaceuticals Inc. at 1-877-446-3679 (1-877-4-INFO-RX) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS ----------

Co-administration o nevirapine extended-release tablets can alter the concentrations o other drugs, and other drugs may alter the concentration o nevirapine. he potential or drug interactions must be considered prior to and during therapy. (5.4, 7, 12.3)

---------- USE IN SPECIFIC POPULATIONS ----------

- No dose adjustment is required or patients with renal impairment with a creatinine clearance greater than or equal to 20 mL per min. Patients on dialysis receive an additional dose o immediate-release nevirapine (200 mg) ollowing each dialysis treatment. (2.5, 8.6)
- Monitor patients with hepatic ibrosis or cirrhosis care ully or evidence o drug-induced toxicity. Do not administer nevirapine extended-release tablets to patients with Child-Pugh B or C. (5.1, 8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

MAY 2015
MXA:NEV1:R1mmh/MXA:MG:NEV1:R1m/MXA:MG:NEV1:R1mh

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FULL PRESCRIBING INFORMATION

WARNING: LIFE-THREATENING (INCLUDING FATAL) HEPATOTOXICITY and SKIN REACTIONS

HEPATOTOXICITY: Severe, life-threatening, and in some cases fatal hepatotoxicity, particularly in the first 18 weeks, has been reported in patients treated with nevirapine. In some cases, patients presented with non-specific prodromal signs or symptoms of hepatitis and progressed to hepatic failure. These events are often associated with rash. Female gender and higher CD4+ cell counts at initiation of therapy place patients at increased risk; women with CD4+ cell counts greater than 250 cells/mm^3, including pregnant women receiving nevirapine in combination with other antiretrovirals for the treatment of HIV-1 infection, are at the greatest risk. However, hepatotoxicity associated with nevirapine use can occur in both genders, all CD4+ cell counts and at any time during treatment. Hepatic failure has also been reported in patients without HIV taking nevirapine for post-exposure prophylaxis (PEP). Use of nevirapine for occupational and non-occupational PEP is contraindicated [see *Contraindications (4.2)*]. Patients with signs or symptoms of hepatitis, or with increased transaminases combined with rash or other systemic symptoms, must discontinue nevirapine and seek medical evaluation immediately [see *Warnings and Precautions (5.1)*].

SKIN REACTIONS: Severe, life-threatening skin reactions, including fatal cases, have occurred in patients treated with nevirapine. These have included cases of Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions characterized by rash, constitutional findings, and organ dysfunction. Patients developing signs or symptoms of severe skin reactions or hypersensitivity reactions must discontinue nevirapine and seek medical evaluation immediately. Transaminase levels should be checked immediately for all patients who develop a rash in the first 18 weeks of treatment. The 14-day lead-in period with immediate-release nevirapine 200 mg daily dosing has been observed to decrease the incidence of rash and must be followed [see *Warnings and Precautions (5.2)*].

MONITORING: Patients must be monitored intensively during the first 18 weeks of therapy with nevirapine to detect potentially life-threatening hepatotoxicity or skin reactions. Extra vigilance is warranted during the first 6 weeks of therapy, which is the period of greatest risk of these events. Do not restart nevirapine following clinical hepatitis, or transaminase elevations combined with rash or other systemic symptoms, or following severe skin rash or hypersensitivity reactions. In some cases, hepatic injury has progressed despite discontinuation of treatment.

1 INDICATIONS AND USAGE

Nevirapine extended-release tablets are indicated or use in combination with other antiretroviral agents or the treatment o HIV-1 in ection in adults and in children 6 to less than 18 years o age [see *Cl n cal Stud es (14 1, 14 2)*].

Additional important in ormation regarding the use o nevirapine extended-release tablets or the treatment o HIV-1 in ection:

- Based on serious and li e-threatening hepatotoxicity observed in controlled and uncontrolled trials, nevirapine should not be initiated in adult emales with CD4 cell counts greater than 250 cells/mm^3 or in adult males with CD4 cell counts greater than 400 cells/mm^3 unless the bene it outweighs the risk [see *Boxed Warn ng and Warn ngs and Precaut ons (5 1)*].
- he 14-day lead-in period with immediate-release nevirapine dosing must be strictly ollowed; it has been demonstrated to reduce the requency o rash [see *Dosage and Adm n strat on (2 5) and Warn ngs and Precaut ons (5 2)*].
- I rash persists beyond the 14-day lead-in period with immediate-release nevirapine, do not begin dosing with nevirapine extended-release tablets. he lead-in dosing with 200 mg once daily immediate-release nevirapine should not be continued beyond 28 days, at which point an alternative regimen should be sought.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Considerations

- Nevirapine extended-release tablets must be swallowed whole and must not be chewed, crushed, or divided.
- Children should be assessed or their ability to swallow tablets be ore prescribing nevirapine extended-release tablets.
- Nevirapine extended-release tablets can be taken with or without ood.
- No recommendations can be made regarding substitution o our nevirapine extended-release 100 mg tablets or one nevirapine extended-release 400 mg tablet.

2.2 Adult Patients

Patients Not Currently Taking Immediate-release Nevirapine: Patients must initiate therapy with one 200 mg tablet o immediate-release nevirapine daily or the irst 14 days in combination with other antiretroviral agents (this lead-in period should be used because it has been ound to lessen the requency o rash), ollowed by one 400 mg tablet o nevirapine extended-release once daily.

Switching Patients from Immediate-release Nevirapine to Nevirapine Extended-release Tablets: Patients already on a regimen o immediate-release nevirapine twice daily in combination with other antiretroviral agents can be switched to nevirapine extended-release tablets 400 mg once daily in combination with other antiretroviral agents without the 14-day lead-in period o immediate-release nevirapine.

2.3 Pediatric Patients

Pediatric patients may be dosed using nevirapine extended-release 400 mg or 100 mg tablets. Nevirapine extended-release tablets are dosed based on a patient s body sur ace area (BSA) calculated using the Mosteller ormula. All pediatric patients must initiate therapy with immediate-release nevirapine (as 150 mg/m^2 o nevirapine oral suspension or as nevirapine tablets), at a dose not to exceed 200 mg per day, administered once daily or the irst 14 days. his lead-in period should be used because it has been demonstrated to reduce the requency o rash. his lead-in period is not required i the patient is already on a regimen o twice daily immediate-release ormulation in combination with other antiretroviral agents.

he recommended oral doses o nevirapine extended-release tablets or pediatric patients 6 to less than 18 years o age based upon their BSA are described in the table below. he total daily dose should not exceed 400 mg or any patient.

Table 1: Recommended Nevirapine Extended-release Tablets Dosing for Pediatric Patients 6 to Less Than 18 Years of Age by BSA After the Lead-in Period with Immediate-release Nevirapine

BSA range (m^2)	Nevirapine Extended-release Tablets Dose (mg)
0.58 to 0.83	200 mg once daily (2 x 100 mg)
0.84 to 1.16	300 mg once daily (3 x 100 mg)
Greater than or equal to 1.17	400 mg once daily (1 x 400 mg)

Mosteller Formula: BSA (m^2) $= \sqrt{\frac{\text{Height (cm)} \times \text{Wt (kg)}}{3600}}$

2.4 Monitoring of Patients

Intensive clinical and laboratory monitoring, including liver enzyme tests, is essential at baseline and during the irst 18 weeks o treatment with nevirapine. he optimal requency o monitoring during this period has not been established. Some experts recommend clinical and laboratory monitoring more o ten than once per month, and in particular, would include monitoring o liver enzyme tests prior to beginning the 14-day lead-in period with immediate-release nevirapine, prior to initiation o nevirapine extended-release tablets, and at 2 weeks a ter initiation o nevirapine extended-release tablets therapy. A ter the initial 18-week period, requent clinical and laboratory monitoring should continue throughout nevirapine extended-release tablets treatment [see *Warn ngs and Precaut ons (5)*]. In some cases, hepatic injury has progressed despite discontinuation o treatment.

Patients already on a regimen o immediate-release nevirapine twice daily who switch to nevirapine extended-release tablets once daily should continue with their ongoing clinical and laboratory monitoring.

2.5 Dosage Adjustment

Patients with Rash: **Discontinue nevirapine if a patient experiences severe rash or any rash accompanied by constitutional findings** [see *Boxed Warn ng and Warn ngs and Precaut ons (5 2)*]**. Do not initiate therapy with nevirapine extended-release tablets if a patient experiences mild to moderate rash without constitutional symptoms during the 14-day lead-in period of immediate-release nevirapine until the rash has resolved** [see *Warn ngs and Precaut ons (5 2)*]**. The total duration of the once daily lead-in dosing period should not exceed 28 days at which point an alternative regimen should be sought.**

Patients with Hepatic Events: **If a clinical (symptomatic) hepatic event occurs, permanently discontinue nevirapine. Do not restart nevirapine after recovery** [see *Warn ngs and Precaut ons (5 1)*].

Patients with Dose Interruption: For patients who interrupt nevirapine extended-release tablets dosing or more than 7 days, restart the recommended lead-in dosing with immediate-release nevirapine, using one 200 mg tablet daily or the irst 14 days.

Patients with Renal Impairment: Patients with CrCL greater than or equal to 20 mL per min and not requiring dialysis do not require an adjustment in dosing. he pharmacokinetics o nevirapine have not been evaluated in patients with CrCL less than 20 mL per min. An additional 200 mg dose o immediate-release nevirapine ollowing each dialysis treatment is indicated in patients requiring dialysis. Nevirapine metabolites may accumulate in patients receiving dialysis; however, the clinical signi icance o this accumulation is not known [see *Cl n cal Pharmacology (12 3)*]. Nevirapine extended-release tablets have not been studied in patients with renal dys unction.

3 DOSAGE FORMS AND STRENGTHS

Nevirapine Extended-release Tablets:

- he 100 mg tablets are white to o -white, round, unscored tablets debossed with **M** on one side o the tablet and **N100** on the other side.

4 CONTRAINDICATIONS

4.1 Hepatic Impairment

Nevirapine extended-release tablets are contraindicated in patients with moderate or severe (Child-Pugh Class B or C, respectively) hepatic impairment [see *Warn ngs and Precaut ons (5 1) and Use n Spec f c Popul ons (8 7)*].

4.2 Post-Exposure Prophylaxis

Nevirapine extended-release tablets are contraindicated or use as part o occupational and non-occupational post-exposure prophylaxis (PEP) regimens [see *Warn ngs and Precaut ons (5 1)*].

5 WARNINGS AND PRECAUTIONS

he most serious adverse reactions associated with nevirapine are hepatitis/hepatic ailure, Stevens- ohnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions. Hepatitis/hepatic ailure may be associated with signs o hypersensitivity which can include severe rash or rash accompanied by ever, general malaise, atigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, acial edema, eosinophilia, granulocytopenia, lymphadenopathy, or renal dys unction.

The first 18 weeks of therapy with nevirapine are a critical period during which intensive clinical and laboratory monitoring of patients is required to detect potentially life-threatening hepatic events and skin reactions. he optimal requency o monitoring during this time period has not been established. Some experts recommend clinical and laboratory monitoring more o ten than once per month, and in particular, include monitoring o liver enzyme tests prior to beginning the 14-day lead-in period with immediate-release nevirapine, prior to initiation o nevirapine extended-release tablets (during the lead-in period), and at 2 weeks a ter initiation o nevirapine extended-release tablets therapy. A ter the initial 18-week period, requent clinical and laboratory monitoring should continue throughout nevirapine extended-release tablets (during the lead-in period), and at 2 weeks a ter initiation o nevirapine extended-release tablets treatment. In addition, the 14-day lead-in period with immediate-release nevirapine has been demonstrated to reduce the requency o rash [see *Dosage and Adm n strat on (2 2, 2 5)*].

Patients already on a regimen o immediate-release nevirapine twice daily who switch to nevirapine extended-release tablets therapy should continue with their ongoing clinical and laboratory monitoring.

5.1 Hepatotoxicity and Hepatic Impairment

Severe, li e-threatening, and in some cases atal hepatotoxicity, including ulminant and cholestatic hepatitis, hepatic necrosis and hepatic ailure, have been reported in patients treated with nevirapine.

he risk o symptomatic hepatic events regardless o severity is greatest in the irst 6 weeks o therapy. he risk continued to be greater in the nevirapine groups in controlled clinical trials through 18 weeks o treatment. However, hepatic events may occur at any time during treatment. In some cases, patients presented with non-speci ic, prodromal signs or symptoms o atigue, malaise, anorexia, nausea, jaundice, liver tenderness or hepatomegaly, with or without initially abnormal serum transaminase levels. Rash was observed in approximately hal o the patients with symptomatic hepatic adverse events. Fever and lu-like symptoms accompanied some o these hepatic events. Some events, particularly those with rash and other symptoms, have progressed to hepatic ailure with transaminase elevation, with or without hyperbilirubinemia, hepatic encephalopathy, prolonged partial thromboplastin time, or eosinophilia. Rhabdomyolysis has been observed in some patients experiencing skin and/or liver reactions associated with nevirapine use. Patients with signs or symptoms o hepatitis must be advised to discontinue nevirapine and immediately seek medical evaluation, which should include liver enzyme tests.

Transaminases should be checked immediately if a patient experiences signs or symptoms suggestive of hepatitis and/or hypersensitivity reaction. Transaminases should also be checked immediately for all patients who develop a rash in the first 18 weeks of treatment. Physicians and patients should be vigilant for the appearance of signs or symptoms of hepatitis, such as fatigue, malaise, anorexia, nausea, jaundice, bilirubinuria, acholic stools, liver tenderness, or hepatomegaly. The diagnosis of hepatotoxicity should be considered in this setting, even if transaminases are initially normal or alternative diagnoses are possible [see *Boxed Warn ng and Dosage and Adm n strat on (2 4)*].

I clinical hepatitis or transaminase elevations combined with rash or other systemic symptoms occur, permanently discontinue nevirapine. Do not restart nevirapine a ter recovery. In some cases, hepatic injury progresses despite discontinuation o treatment.

he patients at greatest risk o hepatic events, including potentially atal events, are women with high CD4 cell counts. In a retrospective analysis o pooled clinical trials with immediate-release nevirapine, during the irst 6 weeks o treatment women had a 3- old higher risk than men or symptomatic, o ten rash-associated, hepatic events (6% versus 2%). Patients with higher CD4 cell counts at initiation o nevirapine therapy are at higher risk or symptomatic hepatic events. Women with CD4 cell counts greater than 250 cells/mm^3 had a 12- old higher risk o symptomatic hepatic adverse events compared to women with CD4 cell counts less than 250 cells/mm^3 (11% versus 1%). An increased risk was observed in men with CD4 cell counts greater than 400 cells/mm^3 (6% versus 1% or men with CD4 cell counts less than 400 cells/mm^3). However, all patients, regardless o gender, CD4 cell count, or antiretroviral treatment history, should be monitored or hepatotoxicity since symptomatic hepatic adverse events have been reported at all CD4 cell counts. Co-in ection with hepatitis B or C and/or increased transaminase elevations at the start o therapy with nevirapine are associated with a greater risk o later symptomatic events (6 weeks or more a ter starting nevirapine) and asymptomatic increases in AS or AL .

In addition, serious hepatotoxicity (including liver ailure requiring transplantation in one instance) has been reported in HIV-1 unin ected individuals receiving multiple doses o nevirapine in the setting o post-exposure prophylaxis (PEP), an unapproved use. Use o nevirapine extended-release tablets or occupational and non-occupational PEP is contraindicated [see *Contra nd cat ons (4 2)*].

Increased nevirapine trough concentrations have been observed in some patients with hepatic ibrosis or cirrhosis. here ore, care ully monitor patients with either hepatic ibrosis or cirrhosis or evidence o drug-induced toxicity. Do not administer nevirapine to patients with moderate or severe (Child-Pugh Class B or C, respectively) hepatic impairment [see *Contra nd cat ons (4 1), Use n Spec f c Popul ons (8 7), and Cl n cal Pharmacology (12 3)*]. Nevirapine extended-release tablets have not been evaluated in subjects with hepatic impairment.

5.2 Skin Reactions

Severe and li e-threatening skin reactions, including atal cases, have been reported in patients taking nevirapine. hese have occurred most requently during the irst 6 weeks o therapy. hese have included cases o Stevens- ohnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions characterized by rash, constitutional indings, and organ dys unction including hepatic ailure. Rhabdomyolysis has been observed in some patients experiencing skin and/or liver reactions associated with nevirapine use.

Patients developing signs or symptoms o severe skin reactions or hypersensitivity reactions (including, but not limited to, severe rash or rash accompanied by ever, general malaise, atigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, acial edema, and/or hepatitis, eosinophilia, granulocytopenia, lymphadenopathy, and renal dys unction) must permanently discontinue nevirapine and seek medical evaluation immediately [see *Boxed Warn ng*]. Do not restart nevirapine ollowing severe skin rash, skin rash combined with increased transaminases or other symptoms, or hypersensitivity reaction.

I patients present with a suspected nevirapine-associated rash, measure transaminases immediately. Permanently discontinue nevirapine in patients with rash-associated transaminase elevations [see *Warn ngs and Precaut ons (5 1)*].

Patients must initiate therapy with immediate-release nevirapine daily or the irst 14 days. his lead-in period has been shown to reduce the requency o rash. Discontinue nevirapine i a patient experiences severe rash or any rash accompanied by constitutional indings. Do not initiate nevirapine extended-release tablets i a patient experiences a mild to moderate rash without constitutional symptoms during the 14-day immediate-release nevirapine lead-in period o 200 mg/day (150 mg/m^2/day in pediatric patients) until the rash has resolved. he total duration o the immediate-release nevirapine lead-in dosing period must not exceed 28 days at which point an alternative regimen should be sought [see *Dosage and Adm n strat on (2 5)*]. Patients must be monitored closely i isolated rash o any severity occurs. Delay in stopping nevirapine treatment a ter the onset o rash may result in a more serious reaction.

Women appear to be at higher risk than men o developing rash with nevirapine.

In a clinical trial o immediate-release nevirapine, concomitant prednisone use (40 mg per day or the irst 14 days o nevirapine administration) was associated with an increase in incidence and severity o rash during the irst 6 weeks o nevirapine therapy. here ore, use o prednisone to prevent nevirapine-associated rash is not recommended.

5.3 Resistance

Nevirapine extended-release tablets must not be used as a single agent to treat HIV-1 or added on as a sole agent to a ailing regimen. Resistant virus emerges rapidly when nevirapine is administered as monotherapy. he choice o new antiretroviral agents to be used in combination with nevirapine should take into consideration the potential or cross-resistance. When discontinuing an antiretroviral regimen containing nevirapine extended-release tablets, the long hal -li e o nevirapine should be taken into account; i antiretrovirals with shorter hal -lives than nevirapine are stopped concurrently, low plasma concentrations o nevirapine alone may persist or a week or longer and virus resistance may subsequently develop [see *M crob ology (12 4)*].

5.4 Drug Interactions

See able 4 or listings o established and potential drug interactions [see *Drug Interact ons (7)*].

Concomitant use o St. ohn s wort (*Hyper cum perforatum*) or St. ohn s wort-containing products and nevirapine is not recommended. Co-administration o St. ohn s wort with non-nucleoside reverse transcriptase inhibitors (NNR Is), including nevirapine, is expected to substantially decrease NNR I concentrations and may result in sub-optimal levels o nevirapine and lead to loss o virologic response and possible resistance to nevirapine or to the class o NNR Is.

Co-administration o nevirapine and e avirenz is not recommended as this combination has been associated with an increase in adverse reactions and no improvement in e icacy.

5.5 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including nevirapine. During the initial phase o combination antiretroviral treatment, patients whose immune system responds may develop an in lammatory response to indolent or residual opportunistic in ections (such as *Mycobacter um av um* in ection, cytomegalovirus, *Pneumocyst s j rovec* pneumonia, or tuberculosis), which may necessitate urther evaluation and treatment.

Autoimmune disorders (such as Graves disease, polymyositis, and Guillain-Barré syndrome) have also been reported to occur in the setting o immune reconstitution, however, the time to onset is more variable, and can occur many months a ter initiation o treatment.

5.6 Fat Redistribution

Redistribution/accumulation o body at including central obesity, dorsocervical at enlargement (bu alo hump), peripheral wasting, acial wasting, breast enlargement, and "cushingoid appearance have been observed in patients receiving antiretroviral therapy. he mechanism and long-term consequences o these events are currently unknown. A causal relationship has not been established.

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience in Adult Patients

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials o a drug cannot be directly compared to rates in the clinical trials o another drug and may not re lect the rates observed in clinical practice.

he most serious adverse reactions associated with nevirapine are hepatitis, hepatic ailure, Stevens- ohnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions. Hepatitis/hepatic ailure may be isolated or associated with signs o hypersensitivity which may include severe rash or rash accompanied by ever, general malaise, atigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, acial edema, eosinophilia, granulocytopenia, lymphadenopathy, or renal dys unction [see *Boxed Warn ng and Warn ngs and Precaut ons (5 1, 5 2)*].

he most common clinical toxicity o nevirapine is rash, which can be severe or li e-threatening [see *Boxed Warn ng and Warn ngs and Precaut ons (5 2)*]. Rash occurs most requently within the irst 6 weeks o therapy. Rashes are usually mild to moderate, maculopapular erythematous cutaneous eruptions, with or without pruritus, located on the trunk, ace and extremities.

he sa ety database in nevirapine extended-release tablets clinical trials contains data rom 800 subjects treated with nevirapine extended-release tablets and 654 subjects treated with immediate release nevirapine.

Trial 1100.1486 (VERxVE): In rial 1100.1486 (VERxVE) treatment-naïve subjects received a lead-in dose o immediate-release nevirapine 200 mg once daily or 14 days (n 1,068) and then were randomized to receive either immediate-release nevirapine 200 mg twice daily (n 506) or nevirapine extended-release tablets 400 mg once daily (n 505). All subjects received teno ovir + emtricitabine as background therapy. Subjects were enrolled with CD4 counts less than 250 cells/mm^3 or women and less than 400 cells/mm^3 or men [see *Ind cat ons and Usage (1)*]. Data on potential symptoms o hepatic events were prospectively collected in this trial. he sa ety data include all subject visits up to the time o the last subject s completion o the 96 week endpoint in the trial (mean observation period 98 weeks).

A ter the lead-in period, the incidence o any hepatic event was 9% in the immediate-release nevirapine group and 6% in the nevirapine extended-release tablets group; the incidence o symptomatic hepatic events (anorexia, jaundice, vomiting) was 3% and 2%, respectively. he incidence o GRADE 3 or 4 AL /AS elevation was 8% in both the immediate-release nevirapine group and nevirapine extended-release tablets group. Overall, there was a comparable incidence o symptomatic hepatic events among men and women enrolled in VERxVE.

Severe or li e-threatening rash considered to be related to nevirapine treatment occurred in 1% o subjects during the lead-in phase with immediate-release nevirapine, and in 1% o subjects in either treatment group during the randomization phase. In addition, six cases o Stevens- ohnson syndrome were reported in the trial; all but one occurred within the irst 30 days o nevirapine treatment.

No Grade 2 or above adverse reactions judged to be related to treatment by the investigator occurred in more than 2% o subjects during the 14-day lead-in with immediate-release nevirapine (200 mg once daily), with the exception o rash which occurred in 4% o subjects.

Adverse reactions o at least moderate intensity (Grades 2 or above) 2% or more o treatment-naïve subjects receiving either immediate-release nevirapine or nevirapine extended-release tablets a ter randomization in rial 1100.1486 are shown in able 2.

Table 2: Selected Clinical Adverse Drug Reactions* of At Least Moderate Intensity (Grade 2 or Above) Occurring in 2% or More of Adult Subjects - Week 96 Analysis of Trial 1100.1486[1]

Adverse Drug Reaction	Nevirapine Immediate-release N = 506 (%)	Nevirapine Extended-release Tablets N = 505 (%)
Rash[2]	4	5
Diarrhea	4	4
Headache	4	4
Clinical Hepatitis[3]	4	2
Abdominal Pain	2	3
Arthralgia	2	2
Pyrexia	2	1
Nausea	2	1
Fatigue	2	2

* Excludes laboratory abnormalities reported as ADRs
Mean observation period 98 weeks.
[2] Rash includes terms rash, rash maculopapular, erythema nodosum, rash erythematous, rash papular, skin reaction, Stevens-ohnson syndrome, drug reaction with eosinophilia and systemic symptoms (DRESS).
[3] Clinical hepatitis includes terms hepatitis, hepatotoxicity, hepatitis acute, liver disorder, hepatitis toxic, hepatic ailure, jaundice.

Laboratory Abnormalities: Liver enzyme test abnormalities (AS , AL) were observed in subjects receiving nevirapine extended-release tablets. Asymptomatic elevations in GG occur requently but are not a contraindication to continue therapy with nevirapine in the absence o elevations in other liver enzyme tests. Laboratory abnormalities that occurred in trial 1100.1486 are shown in able 3.

Table 3: Grade 2 to Grade 4 Laboratory Abnormalities that Represent a Worsening from Baseline Observed in at least 5% of Subjects in Either Treatment Group - Trial 1100.1486

Laboratory Parameter (unit)	Limit	Nevirapine Immediate-release (%) (N = 506)	Nevirapine Extended-release Tablets (%) (N = 505)
Chemistry			
SGP /AL (U/L)			
Grade 2	2.6 to 5.0 x ULN	13	10
Grade 3	5.1 to 10.0 x ULN	3	4
Grade 4	> 10.0 x ULN	4	2
SGO /AS (U/L)			
Grade 2	2.6 to 5.0 x ULN	9	7
Grade 3	5.1 to 10.0 x ULN	2	3
Grade 4	> 10.0 x ULN	2	2
Amylase (U/L)			
Grade 2	1.6 to 2.0 x ULN	4	5
Grade 3	2.1 to 5.0 x ULN	4	2
Grade 4	> 5.0 x ULN	0	< 1
Phosphate (mg/dL)			
Grade 2	2.0 to 2.4 x ULN	38	33
Grade 3	1.0 to 1.9 x ULN	6	7
Grade 4	< 1.0 x ULN	< 1	0
Hematology			
Neutrophils			
Grade 2	750 to 999/mm^3	7	4
Grade 3	500 to 749/mm^3	2	2
Grade 4	< 500/mm^3	1	1
Lipids			
LDL (mg/dL)			
Grade 2	160 to 190 mg/dL	15	15
Grade 3	> 190 mg/dL	5	5
Cholesterol (mg/dL)			
Grade 2	240 to 300 mg/dL	18	19
Grade 3	> 300 mg/dL	4	3

Trial 1100.1526 (TRANxITION): In rial 1100.1526 (RANxI ION) subjects on immediate-release nevirapine 200 mg twice daily or at least 18 weeks were randomized to either receive nevirapine extended-release tablets 400 mg once daily (n 295) or remain on their immediate-release nevirapine treatment (n 148). Adverse reactions observed or nevirapine extended-release tablets subjects (48 week analysis) were similar to those observed in trial 1100.1486, as displayed in able 2.

6.2 Clinical Trial Experience in Pediatric Patients

Adverse reactions were assessed in rial 1100.1518, an open-label, multiple-dose, non-randomized, crossover trial to evaluate the sa ety and steady-state pharmacokinetic parameters o nevirapine extended-release tablets in HIV-1-in ected pediatric subjects 3 to less than 18 years o age. Sa ety was urther examined in an optional extension phase o the trial. Forty subjects who completed the pharmacokinetic part o the trial were treated with nevirapine extended-release tablets once daily in combination with other antiretrovirals or a median duration o 33 weeks. he most requently reported adverse reactions related to nevirapine extended-release tablets in pediatric subjects were similar to those observed in adults. In pediatric subjects the incidence o Grade 2 or higher drug-related rash was 1%. here were no adverse reactions o Grade 2 or above which were considered to be related to treatment by the investigator that occurred in more than 1% o subjects [see *Use n Spec f c Popul ons (8 4), Cl n cal Pharmacology (12 3), and Cl n cal Stud es (14 2)*].

6.3 Post-Marketing Experience

he ollowing adverse reactions have been identi ied during post-approval use o immediate-release nevirapine. Because these reactions are reported voluntarily rom a population o uncertain size, it is not always possible to reliably estimate their requency or establish a causal relationship to drug exposure.

Body as a Whole: ever, somnolence, drug withdrawal [see *Drug Interact ons (7)*], redistribution/accumulation o body at [see *Warn ngs and Precaut ons (5 6)*]

Gastrointestinal: vomiting

Liver and Biliary: jaundice, ulminant and cholestatic hepatitis, hepatic necrosis, hepatic ailure

Hematology: anemia, eosinophilia, neutropenia

Investigations: decreased serum phosphorus

***Musculosk

This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

Do not administer nevirapine to patients with moderate or severe (Child-Pugh Class B or C, respectively) hepatic impairment [*see Contra nd cat ons (4), Warn ngs and Precaut ons (5 1), and Use n Spec f c Populat ons (8 7)*]. Nevirapine extended-release tablets have not been evaluated in patients with hepatic impairment.

Gender In the multinational 2NN trial o immediate-release nevirapine, a population pharmacokinetic substudy o 1,077 subjects was per ormed that included 391 emales. Female subjects showed a 13.8% lower clearance o nevirapine than did men. Since neither body weight nor Body Mass Index (BMI) had an in luence on the clearance o nevirapine, the e ect o gender cannot solely be explained by body size.

he e ects o gender on the pharmacokinetics o nevirapine extended-release tablets have been investigated in rial 1100.1486. Female subjects tend to have higher (approximately 20% to 30%) trough concentrations in both nevirapine extended-release tablets and immediate-release nevirapine treatment groups.

Race An evaluation o nevirapine plasma concentrations (pooled data rom several clinical trials) rom HIV-1-in ected subjects (27 Black, 24 Hispanic, 189 Caucasian) revealed no marked di erence in nevirapine steady-state trough concentrations (median C_{min} 4.7 mcg per mL Black, 3.8 mcg per mL Hispanic, 4.3 mcg per mL Caucasian) with long-term treatment with immediate-release nevirapine at 400 mg per day. However, the pharmacokinetics o nevirapine have not been evaluated speci ically or the e ects o ethnicity.

Black subjects (n 80/group) in rial 1100.1486 showed approximately 30% to 35% higher trough concentrations than Caucasian subjects (250 to 325 subjects/group) in both immediate-release nevirapine and nevirapine extended-release tablets treatment groups over 96 weeks o treatment at 400 mg per day.

Ger atr c Pat ents Nevirapine pharmacokinetics in HIV-1-in ected adults do not appear to change with age (range 18 to 68 years); however, nevirapine has not been extensively evaluated in patients beyond the age o 65 years [*see Use n Spec f c Populat ons (8 5)*].

Ped atr c Pat ents he pharmacokinetics o nevirapine extended-release tablets were assessed in HIV-1 in ected children 3 to less than 18 years o age. Children enrolled received weight or body sur ace area dose-adjusted immediate-release nevirapine in combination with other antiretrovirals or a minimum o 18 weeks and then were switched to nevirapine extended-release tablets in combination with other antiretrovirals or 10 days, a ter which steady-state pharmacokinetic parameters were determined.

Overall, the mean systemic nevirapine exposures in children 6 to less than 18 years o age ollowing administration o nevirapine extended-release tablets and immediate-release nevirapine were similar. Based on intensive PK data (N 17), the observed geometric mean ratios o nevirapine extended-release tablets to immediate-release nevirapine were approximately 97% or C_{min} and 94% or AUC with 90% con idence intervals within 80% to 125%; the ratio or C_{max} was lower and consistent with a once daily extended-release dosage orm.

rial 1100.1518 did not provide su icient pharmacokinetic data or children 3 to less than 6 years o age to support the use o nevirapine extended-release tablets in this age group.

Drug Interactions: [*See Drug Interact ons (7).*]

Nevirapine induces hepatic cytochrome P450 metabolic isoenzymes 3A and 2B6. Co-administration o nevirapine extended-release tablets and drugs primarily metabolized by CYP3A or CYP2B6 may result in decreased plasma concentrations o these drugs and attenuate their therapeutic e ects.

While primarily an inducer o cytochrome P450 3A and 2B6 enzymes, nevirapine may also inhibit this system. Among human hepatic cytochrome P450s, nevirapine was capable *n v tro* o inhibiting the 10-hydroxylation o (R)-war arin (CYP3A). he estimated Ki or the inhibition o CYP3A was 270 micromolar, a concentration that is unlikely to be achieved in patients as the therapeutic range is less than 25 micromolar. here ore, nevirapine may have minimal inhibitory e ect on other substrates o CYP3A.

Nevirapine does not appear to a ect the plasma concentrations o drugs that are substrates o other CYP450 enzyme systems, such as 1A2, 2D6, 2A6, 2E1, 2C9, or 2C19.

able 5 (see below) contains the results o drug interaction trials per ormed with immediate-release nevirapine and other drugs likely to be co-administered. he e ects o nevirapine on the AUC, C_{max} and C_{min} o co-administered drugs are summarized. Results o drug interaction studies with immediate-release nevirapine are expected to also apply to nevirapine extended-release tablets.

Table 5: Drug Interactions: Changes in Pharmacokinetic Parameters for Co-administered Drug in the Presence of Immediate-release Nevirapine (All Interaction Studies Were Conducted in HIV-1 Positive Subjects)

Co-administered Drug	Dose of Co-administered Drug	Dose Regimen of Immediate-release Nevirapine	n	% Change of Co-administered Drug Pharmacokinetic Parameters (90% CI)		
Antiretrovirals				AUC	C_{max}	C_{min}
Atazanavir/ Ritonavir[a d]	300 mg/ 100 mg QD day 4 to 13, then 400 mg/ 100 mg QD, day 14 to 23	200 mg BID day 1 to 23. Subjects were treated with nevirapine prior to trial entry.	23	Atazanavir 300 mg/ 100 mg ↓42 (↓52 to ↓29)	Atazanavir 300 mg/ 100 mg ↓28 (↓40 to ↓14)	Atazanavir 300 mg/ 100 mg ↓72 (↓80 to ↓60)
				Atazanavir 400 mg/ 100 mg ↓19 (↓35 to ↑2)	Atazanavir 400 mg/ 100 mg ↑2 (↓15 to ↑24)	Atazanavir 400 mg/ 100 mg ↓59 (↓73 to ↓40)
Darunavir/ Ritonavir	400 mg/ 100 mg BID	200 mg BID	8	↑24 (↓3 to ↑57)	↑40 (↑14 to ↑73)	↑2 (↓21 to ↑32)
Didanosine	100 mg to 150 mg BID	200 mg QD x 14 days; 200 mg BID x 14 days	18	↔	↔	§
E avirenz[a]	600 mg QD	200 mg QD x 14 days; 400 mg QD x 14 days	17	↓28 (↓34 to ↓14)	↓12 (↓23 to ↑1)	↓32 (↓35 to ↓19)
Fosamprenavir	1400 mg BID	200 mg BID. Subjects were treated with nevirapine prior to trial entry.	17	↓33 (↓45 to ↓20)	↓25 (↓37 to ↓10)	↓35 (↓50 to ↓15)
Fosamprenavir/ Ritonavir	700 mg/ 100 mg BID	200 mg BID. Subjects were treated with nevirapine prior to trial entry	17	↓11 (↓23 to ↑3)	↔	↓19 (↓32 to ↓4)
Indinavir[a]	800 mg q8H	200 mg QD x 14 days; 200 mg BID x 14 days	19	↓31 (↓39 to ↓22)	↓15 (↓24 to ↓4)	↓44 (↓53 to ↓33)
Lopinavir[a b]	300 mg/75 mg/m² (lopinavir/ritonavir)[b]	7 mg/kg or 4 mg/kg QD x 2 weeks; BID x one week	12, 15	↓22 (↓44 to ↑9)	↓14 (↓36 to ↑16)	↓55 (↓75 to ↓19)
Lopinavir[a]	400 mg/ 100 mg BID (lopinavir/ ritonavir)	200 mg QD x 14 days; 200 mg BID > one year	22, 19	↓27 (↓47 to ↓2)	↓19 (↓38 to ↑5)	↓51 (↓72 to ↓26)
Maraviroc[f]	300 mg SD	200 mg BID	8	↑1 (↓35 to ↑55)	↑54 (↓6 to ↑151)	↔
Nel inavir[a]	750 mg ID	200 mg QD x 14 days; 200 mg BID x 14 days	23	↔	↔	↓32 (↓50 to ↑5)
Nel inavir-M8 metabolite				↓62 (↓70 to ↓53)	↓59 (↓68 to ↓48)	↓66 (↓74 to ↓55)
Ritonavir	600 mg BID	200 mg QD x 14 days; 200 mg BID x 14 days	18	↔	↔	↔
Stavudine	30 mg to 40 mg BID	200 mg QD x 14 days; 200 mg BID x 14 days	22	↔	↔	§
Zalcitabine	0.125 mg to 0.25 mg ID	200 mg QD x 14 days; 200 mg BID x 14 days	6	↔	↔	§
Zidovudine	100 mg to 200 mg ID	200 mg QD x 14 days; 200 mg BID x 14 days	11	↓28 (↓40 to ↓4)	↓30 (↓51 to ↑14)	§
Other Medications				AUC	C_{max}	C_{min}
Clarithromycin[a]	500 mg BID	200 mg QD x 14 days; 200 mg BID x 14 days	15	↓31 (↓38 to ↓24)	↓23 (↓31 to ↓14)	↓56 (↓70 to ↓36)
Metabolite 14-OH-clarithromycin				↑42 (↑16 to ↑73)	↑47 (↑21 to ↑80)	↔
Ethinyl estradiol[a] and	0.035 mg (as Ortho-Novum® 1/35)	200 mg QD x 14 days; 200 mg BID x 14 days	10	↓20 (↓33 to ↓3)	↔	§
Norethindrone[a]	1 mg (as Ortho-Novum® 1/35)			↓19 (↓30 to ↓7)	↓16 (↓27 to ↓3)	§
Depomedroxy-progesterone acetate	150 mg every 3 months	200 mg QD x 14 days; 200 mg BID x 14 days	32	↔	↔	↔
Fluconazole	200 mg QD	200 mg QD x 14 days; 200 mg BID x 14 days	19	↔	↔	↔
Ketoconazole[a]	400 mg QD	200 mg QD x 14 days; 200 mg BID x 14 days	21	↓72 (↓80 to ↓60)	↓44 (↓58 to ↓27)	§
Methadone[a]	Individual Subject Dosing	200 mg QD x 14 days; 200 mg BID ≥ 7 days	9	In a controlled pharmacokinetic trial with nine subjects receiving chronic methadone to whom steady-state nevirapine therapy was added, the clearance o methadone was increased by 3- old, resulting in symptoms o withdrawal, requiring dose adjustments in 10 mg segments, in seven o the nine subjects. Methadone did not have any e ect on nevirapine clearance.		
Ri abutin[a]	150 mg or 300 mg QD	200 mg QD x 14 days; 200 mg BID x 14 days	19	↑17 (↓2 to ↑40)	↑28 (↑9 to ↑51)	↔
Metabolite 25-O-desacetyl-ri abutin				↑24 (↓16 to ↑84)	↑29 (↓2 to ↑68)	↑22 (↓14 to ↑74)
Ri ampin[a]	600 mg QD	200 mg QD x 14 days; 200 mg BID x 14 days	14	↑11 (↓4 to ↑28)	↔	§

§ C_{min} below detectable level o the assay
↑ Increase, ↓ Decrease, ↔ No E ect
[a] For in ormation regarding clinical recommendations, see Drug Interactions (7).
[b] Pediatric subjects ranging in age rom 6 months to 12 years
Parallel group design; n or nevirapine + lopinavir/ritonavir, n or lopinavir/ritonavir alone.
[d] Parallel group design; n 23 or atazanavir/ritonavir + nevirapine, n 22 or atazanavir/ritonavir without nevirapine. Changes in atazanavir PK are relative to atazanavir/ritonavir 300 mg/100 mg alone.
Based on between-trial comparison.
[f] Based on historical controls.

Because o the design o the drug interaction trials (addition o 28 days o nevirapine therapy to existing HIV-1 therapy), the e ect o the concomitant drug on plasma nevirapine steady-state concentrations was estimated by comparison to historical controls.

Administration o ri ampin had a clinically signi icant e ect on nevirapine pharmacokinetics, decreasing AUC and C_{max} by greater than 50%. Administration o luconazole resulted in an approximate 100% increase in nevirapine exposure, based on a comparison to historic data [*see Drug Interact ons (7)*]. he e ect o other drugs listed in able 5 on nevirapine pharmacokinetics was not signi icant. No signi icant interaction was observed when tipranavir was co-administered with low-dose ritonavir and nevirapine.

12.4 Microbiology

Mechanism of Action: Nevirapine is a non-nucleoside reverse transcriptase inhibitor (NNR I) o HIV-1. Nevirapine binds directly to reverse transcriptase (R) and blocks the RNA-dependent and DNA-dependent DNA polymerase activities by causing a disruption o the enzyme's catalytic site. he activity o nevirapine does not compete with template or nucleoside triphosphates. HIV-2 R and eukaryotic DNA polymerases (such as human DNA polymerases α, β, γ, or δ) are not inhibited by nevirapine.

Antiviral Activity: he antiviral activity o nevirapine has been measured in a variety o cell lines including peripheral blood mononuclear cells, monocyte-derived macrophages, and lymphoblastoid cell lines. In an assay using human embryonic kidney 293 cells, the median EC_{50} value (50% inhibitory concentration) o nevirapine was 90 nM against a panel o 2,923 wild-type isolates o HIV-1 that were primarily (93%) clade B clinical isolates rom the United States. he 99th percentile EC_{50} value was 470 nM in this trial. he median EC_{50} value was 63 nM (range 14-302 nM, n 29) against clinical isolates o HIV-1 clades A, B, C, D, F, G, and H, and circulating recombinant orms CRF01_AE, CRF02_AG and CRF12_BF. Nevirapine had no antiviral activity in cell culture against group O HIV-1 isolates (n 3) or HIV-2 isolates (n 3) replicating in cord blood mononuclear cells. Nevirapine in combination with e avirenz exhibited strong antagonistic anti-HIV-1 activity in cell culture and was additive to antagonistic with the protease inhibitor ritonavir or the usion inhibitor en uvirtide. Nevirapine exhibited additive to synergistic anti-HIV-1 activity in combination with the protease inhibitors amprenavir, atazanavir, indinavir, lopinavir, nel inavir, saquinavir and tipranavir, and the NR Is abacavir, didanosine, emtricitabine, lamivudine, stavudine, teno ovir and zidovudine. he anti-HIV-1 activity o nevirapine was antagonized by the anti-HBV drug ade ovir and by the anti-HCV drug ribavirin in cell culture.

Resistance: HIV-1 isolates with reduced susceptibility (100- to 250- old) to nevirapine emerge in cell culture. Genotypic analysis showed mutations in the HIV-1 R gene encoding Y181C and/or V106A substitutions depending upon the virus strain and cell line employed. ime to emergence o nevirapine resistance in cell culture was not altered when selection included nevirapine in combination with several other NNR Is.

Phenotypic and genotypic changes in HIV-1 isolates rom treatment-naïve subjects receiving either nevirapine (n 24) or nevirapine and zidovudine (n 14) were monitored in Phase 1 and 2 trials ranging rom 1 to 12 weeks or longer. A ter one week o nevirapine monotherapy, isolates rom 3/3 subjects had decreased susceptibility to nevirapine in cell culture. One or more o the R mutations resulting in amino acid substitutions K103N, V106A, V108I, Y181C, Y188C, and G190A were detected in HIV-1 isolates rom some subjects as early as 2 weeks a ter therapy initiation. By week 8 o nevirapine monotherapy, 100% o the subjects tested (n 24) had HIV-1 isolates with a greater than 100- old decrease in susceptibility to nevirapine in cell culture compared to baseline, and had one or more o the nevirapine-associated R resistance substitutions. Nineteen o these subjects (80%) had isolates with Y181C substitutions regardless o dose.

Genotypic analysis o isolates rom antiretroviral-naïve subjects experiencing virologic ailure (n 71) receiving nevirapine once daily (n 25) or twice daily (n 46) in combination with lamivudine and stavudine (trial 2NN) or 48 weeks showed that isolates rom 8/25 and 23/46 subjects, respectively, contained one or more o the ollowing NNR I resistance-associated substitutions: Y181C, K101E, G190A/S, K103N, V106A/M, V108I, Y188C/L, A98G, F227L, and M230L.

For trial 1100.1486, genotypic analysis was per ormed or baseline and on-therapy isolates rom 23 and 34 subjects who experienced virologic ailure in the nevirapine extended-release tablets and immediate-release nevirapine treatment group, respectively. Nevirapine resistance-associated substitutions developed in the on-therapy isolates o 78% (18/23) o the subjects who had virologic ailures in the nevirapine extended-release tablets treatment group and 88% (30/34) o the subjects in the immediate-release nevirapine treatment group, respectively. he Y181C nevirapine resistance-associated substitution was ound alone or in combination with other nevirapine resistance-associated substitutions (K101E, K103N, V106A, V108I, V179D/E/I, Y188 C/F/H/L/N, G190A, P225H, F227L, M230L) in isolates rom 14 subjects ailing nevirapine extended-release tablets treatment and 25 subjects ailing immediate-release nevirapine treatment. On-therapy isolates rom one subject in nevirapine extended-release tablets treatment group developed a novel amino acid substitution Y181I and isolates rom another subject in the immediate-release nevirapine treatment group developed a novel amino acid substitution Y188N. Phenotypic analysis showed that Y188N and Y181I substitutions con erred 103- and 22- old reductions in susceptibility to nevirapine, respectively.

Cross-resistance: Rapid emergence o HIV-1 strains which are cross-resistant to NNR Is has been observed in cell culture. Nevirapine-resistant HIV-1 isolates were cross-resistant to the NNR Is delavirdine, e avirenz, and etravirine. he Y188N con erred 22- and 7- old reductions in susceptibility to delavirdine and e avirenz, respectively, but showed no decrease in susceptibility to etravirine. Similarly, the Y181I substitution reduced susceptibility to delavirdine and etravirine 3-and 8- old, respectively, but did not reduce susceptibility to e avirenz. However, nevirapine-resistant isolates were susceptible to the NR Is ddI and ZDV. Similarly, ZDV-resistant isolates were susceptible to nevirapine in cell culture.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Long-term carcinogenicity studies in mice and rats were carried out with nevirapine. Mice were dosed with 0, 50, 375 or 750 mg/kg/day or 2 years. Hepatocellular adenomas and carcinomas were increased at all doses in males and at the two high doses in emales. In studies in which rats were administered nevirapine at doses o 0, 3.5, 17.5 or 35 mg/kg/day or 2 years, an increase in hepatocellular adenomas was seen in males at all doses and in emales at the high dose. he systemic exposure (based on AUCs) at all doses in the two animal studies was lower than that measured in humans at the 200 mg twice daily dose o immediate-release nevirapine. he mechanism o the carcinogenic potential is unknown.

Mutagenesis: However, in genetic toxicology assays, nevirapine showed no evidence o mutagenic or clastogenic activity in a battery o *n v tro* and *n v vo* studies. hese included microbial assays or gene mutation (Ames: Salmonella strains and E. coli), mammalian cell gene mutation assay (CHO/HGPR), cytogenetic assays using a Chinese hamster ovary cell line and a mouse bone marrow micronucleus assay ollowing oral administration. Given the lack o genotoxic activity o nevirapine, the relevance to humans o hepatocellular neoplasms in nevirapine-treated mice and rats is not known.

Impairment of Fertility: In reproductive toxicology studies, evidence o impaired ertility was seen in emale rats at doses providing systemic exposure, based on AUC, approximately equivalent to that provided with the recommended clinical dose.

13.2 Animal Toxicology and/or Pharmacology

Animal studies have shown that nevirapine is widely distributed to nearly all tissues and readily crosses the blood-brain barrier.

14 CLINICAL STUDIES

14.1 Adult Patients

he clinical e icacy o nevirapine extended-release tablets is based on 96-week data rom an ongoing, randomized, double-blind, double-dummy Phase 3 trial (rial 1100.1486, VERxVE) in treatment-naïve subjects and on 48-week data in an ongoing, randomized, open-label trial in subjects who switched rom immediate-release nevirapine tablets administered twice daily to nevirapine extended-release tablets administered once daily (rial 1100.1526, RANxI ION).

Treatment-naïve Subjects: rial 1100.1486 (VERxVE) is a Phase 3 trial in which treatment-naïve subjects received immediate-release nevirapine 200 mg once daily or 14 days and then were randomized to receive either immediate-release nevirapine 200 mg twice daily or nevirapine extended-release tablets 400 mg once daily. All subjects received teno ovir + emtricitabine as background therapy. Randomization was strati ied by screening HIV-1 RNA level (less than or equal to 100,000 copies per mL and greater than 100,000 copies per mL). Subject demographic and baseline disease characteristics were balanced between the two treatment groups. With respect to demographics: 85% o the subjects were male, 75% were white, 20% were black, and approximately 29% were rom North America. With respect to baseline disease characteristics: mean viral load was 4.7 log copies per mL, mean CD4 cell count was 228 cells/mm³ and 73% o subjects had clade B HIV-1 subtype. Approximately two-thirds o the subjects had a baseline HIV-RNA level o less than or equal to 100,000 copies per mL.

able 6 describes week 96 outcomes in the rial 1100.1486 (VERxVE). hese outcomes include all subjects who were randomized a ter the 14 day lead-in with immediate-release nevirapine and received at least one dose o blinded study medication.

Table 6: Outcomes at Week 96 in Trial 1100.1486

	Week 96	
	Nevirapine Immediate-release N = 506	Nevirapine Extended-release Tablets N = 505
Virologic Success - HIV RNA < 50 copies/mL	67%	69%
Virologic Failure[#]	18%	17%
No Virologic Data at Week 96 Window		
Reasons		
Discontinued trial/study drug due to adverse event or death[*]	10%	8%
Discontinued trial/study drug or other reasons[**]	5%	5%
Missing data during window but on trial	< 1%	1%

[#] Includes subjects who changed optimized background therapy (OB) to new class or changed OB not permitted per protocol or due to lack o e icacy prior to Week 96, subjects who discontinued prior to Week 96 or lack or loss o e icacy and subjects with HIV RNA greater than or equal to 50 copies/mL in the Week 96 window.
[*] Includes subjects who discontinued due to adverse events or death at any time point rom Day 1 through the Week 96 window i this resulted in no virologic data on treatment during the speci ied window.
[**] Other includes: withdrew consent, lost to ollow-up, moved away, etc.

At 96 weeks, mean change rom baseline in CD4 cell count adjusting or baseline HIV-1 viral load stratum was 222 cells/mm³ and 244 cells/mm³ or the groups receiving immediate-release nevirapine and nevirapine extended-release tablets, respectively.

Subjects Switching from Immediate-release Nevirapine to Nevirapine Extended-release Tablets: rial 1100.1526 (RANxI ION) is a Phase 3 trial to evaluate sa ety and antiviral activity o switching rom immediate-release nevirapine to nevirapine extended-release tablets. In this open-label trial, 443 subjects already on an antiviral regimen containing immediate-release nevirapine 200 mg twice daily with HIV-1 RNA less than 50 copies per mL were randomized in a 2:1 ratio to nevirapine extended-release tablets 400 mg once daily or immediate-release nevirapine 200 mg twice daily. Approximately hal o the subjects had teno ovir + emtricitabine as their background therapy, with the remaining subjects receiving abacavir sul ate + lamivudine or zidovudine + lamivudine. Approximately hal o the subjects had at least 3 years o exposure to immediate-release nevirapine prior to entering the trial.

At 48 weeks a ter randomization in rial 1100.1526, 91% o subjects receiving immediate-release nevirapine 200 mg twice daily and 93% o subjects receiving nevirapine extended-release tablets 400 mg once daily continued to have HIV-1 RNA less than 50 copies per mL.

14.2 Pediatric Patients

rial 1100.1518 was an open-label, multiple-dose, non-randomized, crossover trial per ormed in 85 HIV-1 in ected pediatric subjects 3 to less than 18 years o age who had received at least 18 weeks o immediate-release nevirapine and had plasma HIV-1 RNA less than 50 copies per mL prior to trial enrollment. Subjects were strati ied according to age (3 to less than 6 years, 6 to less than 12 years, and 12 to less than 18 years). Following a 10-day period with immediate-release nevirapine, subjects were treated with nevirapine extended-release tablets once daily in combination with other antiretrovirals or 10 days, a ter which steady-state pharmacokinetic parameters were determined. Forty o the 80 subjects who completed the initial part o the study were enrolled in an optional extension phase o the trial which evaluated the sa ety and antiviral activity o nevirapine extended-release tablets through a minimum o 24 weeks o treatment. Zidovudine or stavudine plus lamivudine were the most commonly used background therapies in subjects who entered the optional extension phase.

Baseline demographics included: 55% o the subjects were emale, 93% were black, 7% were white, and approximately 84% were rom A rica. Subjects had a median baseline CD4 cell count o 925 cells/mm³ (range 207 to 2057 cells/mm³).

O the 40 subjects who entered the treatment extension phase, 39 completed at least 24 weeks o treatment and one subject discontinued prematurely due to an adverse reaction. A ter 24 weeks or more o treatment with nevirapine extended-release tablets, all 39 subjects continued to have plasma HIV-1 RNA less than 50 copies per mL. Median CD4 cell counts or the 3 to less than 6 year, 6 to less than 12 year, and 12 to less than 18 year age groups were 1113 cells/mm³, 853 cells/mm³, and 682 cells/mm³, respectively. hese CD4 cell counts were similar to those observed at baseline.

16 HOW SUPPLIED/STORAGE AND HANDLING

Nevirapine Extended-release ablets are available containing 100 mg o nevirapine, USP.

he 100 mg tablets are white to o -white, round, unscored tablets debossed with **M** on one side o the tablet and **N100** on the other side. hey are available as ollows:

NDC 0378-6950-93
bottles o 30 tablets

NDC 0378-6950-77
bottles o 90 tablets

NDC 0378-6950-05
bottles o 500 tablets

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

Store in a sa e place out o the reach o children.

Dispense in a tight, light-resistant container as de ined in the USP using a child-resistant closure.

PHARMACIST: Dispense a Medication Guide with each prescription.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

- **Hepatotoxicity and Skin Reactions**

Inform patients of the possibility of severe liver disease or skin reactions associated with nevirapine that may result in death. Instruct patients developing signs or symptoms of liver disease or severe skin reactions to discontinue nevirapine and seek medical attention immediately, including performance of laboratory monitoring. Symptoms of liver disease include fatigue, malaise, anorexia, nausea, jaundice, acholic stools, liver tenderness or hepatomegaly. Symptoms of severe skin or hypersensitivity reactions include rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, and/or hepatitis.

Intensive clinical and laboratory monitoring, including liver enzymes, is essential during the irst 18 weeks o therapy with nevirapine to detect potentially li e-threatening hepatotoxicity and skin reactions. However, liver disease can occur a ter this period; there ore, monitoring should continue at requent intervals throughout nevirapine treatment. Extra vigilance is warranted during the irst 6 weeks o therapy, which is the period o greatest risk o hepatic events and skin reactions. Advise patients with signs and symptoms o hepatitis to discontinue nevirapine and seek medical evaluation immediately. I nevirapine is discontinued due to hepatotoxicity, do not restart it. Patients, particularly women, with increased CD4 cell count at initiation o nevirapine therapy (greater than 250 cells/mm³ in women and greater than 400 cells/mm³ in men) are at substantially higher risk or development o symptomatic hepatic events, o ten associated with rash. Advise patients that co-in ection with hepatitis B or C and/or increased transaminases at the start o therapy with nevirapine are associated with a greater risk o later symptomatic events (6 weeks or more a ter starting nevirapine) and asymptomatic increases in AS or AL [*see Boxed Warn ng and Warn ngs and Precaut ons (5 1)*].

he majority o rashes associated with nevirapine occur within the irst 6 weeks o initiation o therapy. Instruct patients that i any rash occurs during the 2-week lead-in period with immediate-release nevirapine, do not initiate nevirapine extended-release tablets until the rash resolves. he total duration o the lead-in dosing period with immediate-release nevirapine should not exceed 28 days, at which point an alternative regimen may need to be started. Any patient experiencing a rash should have their liver enzymes (AS , AL) evaluated immediately. Patients with severe rash or hypersensitivity reactions should discontinue nevirapine immediately and consult a physician. Nevirapine should not be restarted ollowing severe skin rash or hypersensitivity reaction. Women tend to be at higher risk or development o nevirapine-associated rash. For patients who interrupt nevirapine extended-release tablets dosing or more than 7 days and or whom restarting nevirapine therapy is not contraindicated, restart the recommended lead-in dosing with immediate-release nevirapine using one 200 mg tablet daily (150 mg/m²/day in pediatric patients) or the irst 14 days [*see Boxed Warn ng, Dosage and Adm n strat on (2 5), and Warn ngs and Precaut ons (5 2)*].

- **Administration**

In orm patients to take nevirapine extended-release tablets every day as prescribed. Patients should not alter the dose without consulting their doctor. I a dose is missed, patients should take the next dose as soon as possible. However, i a dose is skipped, the patient should not double the next dose. Advise patients to report to their doctor the use o any other medications.

Instruct patients to swallow nevirapine extended-release tablets whole. hey must not be chewed, crushed, or divided.

Nevirapine extended-release tablets are not a cure or HIV-1 in ection; patients may continue to experience illnesses associated with advanced HIV-1 in ection, including opportunistic in ections. Advise patients to remain under the care o a physician when using nevirapine extended-release tablets.

Patients should be told that sustained decreases in plasma HIV RNA have been associated with a reduced risk o progression to AIDS and death.

Advise patients to avoid doing things that can spread HIV-1 in ection to others:

- **Do not share needles or other injection equipment.**
- **Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.**
- **Do not have any kind of sex without protection.** Always practice sa e sex by using a latex or polyurethane condom to lower the chance o sexual contact with semen, vaginal secretions, or blood.
- **Do not breastfeed.** We do not know i nevirapine can be passed to your baby in your breast milk and whether it could harm your baby. Also, mothers with HIV-1 should not breast eed because HIV-1 can be passed to the baby in the breast milk.

In orm patients that they may occasionally see so t remnants o nevirapine extended-release tablets in their stool, which sometimes resemble intact tablets. hese occurrences have not been shown to a ect drug levels or response.

- **Drug Interactions**

Nevirapine extended-release tablets may interact with some drugs; there ore, patients should be advised to report to their doctor the use o any other prescription, non-prescription medication or herbal products, particularly St. ohn s wort [*see Warn ngs and Precaut ons (5 4) and Drug Interact ons (7)*].

- **Contraceptives**

Hormonal methods o birth control, other than depomedroxy-progesterone acetate (DMPA), should not be used as the sole method o contraception in women taking nevirapine extended-release tablets, since nevirapine extended-release tablets may lower the plasma levels o these medications. Additionally, when oral contraceptives are used or hormonal regulation during nevirapine extended-release tablets therapy, the therapeutic e ect o the hormonal therapy should be monitored [*see Drug Interact ons (7)*].

- **Methadone**

Nevirapine extended-release tablets may decrease plasma concentrations o methadone by increasing its hepatic metabolism. Narcotic withdrawal syndrome has been reported in patients treated with nevirapine and methadone concomitantly. Monitor methadone-maintained patients beginning nevirapine therapy or evidence o withdrawal and adjust methadone dose accordingly [*see Drug Interact ons (7)*].

- **Fat Redistribution**

In orm patients that redistribution or accumulation o body at may occur in patients receiving antiretroviral therapy and that the cause and long-term health e ects o these conditions are not known at this time [*see Warn ngs and Precaut ons (5 6)*].

MEDICATION GUIDE
NEVIRAPINE EXTENDED-RELEASE TABLETS
(ne vir′ a peen)
100 mg

Read this Medication Guide before you start taking nevirapine extended-release tablets and each time you get a refill. There may be new information. This information does not take the place of talking to your doctor about your medical condition or treatment.

What is the most important information I should know about nevirapine?

Nevirapine can cause serious side effects. These include severe liver and skin problems that can cause death. These problems can happen at any time during treatment, but your risk is higher during the first 18 weeks of treatment.

1. **Severe liver problems:** Anyone who takes nevirapine may get severe liver problems. In some cases these liver problems can lead to liver failure and the need for a liver transplant, or death.

People who have a higher CD4⁺ cell count when they begin nevirapine treatment have a higher risk of liver problems, especially:

- Women with CD4⁺ counts higher than 250 cells/mm³. This group has the highest risk.
- Men with CD4⁺ counts higher than 400 cells/mm³.

If you are a woman with CD4⁺ counts higher than 250 cells/mm³ or a man with CD4⁺ counts higher than 400 cells/mm³, you and your doctor will decide whether starting nevirapine is right for you.

In general, women have a higher risk of liver problems compared to men.

People who have abnormal liver test results before starting nevirapine treatment and people with hepatitis B or C also have a greater risk of getting liver problems.

You may get a rash if you have liver problems.

Stop taking nevirapine and call your doctor right away if you have any of the following symptoms of liver problems:

- dark (tea colored) urine
- yellowing of your skin or whites of your eyes
- light-colored bowel movements (stools)
- fever
- nausea (feeling sick to your stomach)
- feel unwell or like you have the flu
- pain or tenderness on your right side below your ribs
- tiredness
- loss of appetite

Your doctor should see you and do blood tests often to check your liver function during the first 18 weeks of treatment with nevirapine. You should continue to have your liver checked regularly during your treatment with nevirapine. It is important for you to keep all of your doctor appointments.

2. **Severe rash and skin reactions:** Skin rash is the most common side effect of nevirapine. Most rashes happen in the first 6 weeks of taking nevirapine. **Rashes and skin reactions may be severe, life-threatening, and in some people, may lead to death. Stop using nevirapine and call your doctor right away if you get a rash with any of the following symptoms:**

- blisters
- mouth sores
- red or inflamed eyes, like "pink eye" (conjunctivitis)
- liver problems (see symptoms of liver problems above)
- swelling of your face
- fever
- feel unwell or like you have the flu
- tiredness
- muscle or joint aches

If your doctor tells you to stop treatment with nevirapine because you have had any of the serious liver or skin problems described above, you should never take nevirapine again.

See the section **"What are the possible side effects of nevirapine?"** for more information.

What is nevirapine?

- Nevirapine tablets and nevirapine oral solution are prescription HIV medicines used with other HIV medicines to treat HIV (Human Immunodeficiency Virus). HIV is the virus that causes AIDS (Acquired Immune Deficiency Syndrome).
- Nevirapine extended-release tablets are a prescription medicine used with other HIV medicines to treat HIV (Human Immunodeficiency Virus) in adults and in children who are 6 years of age to less than 18 years of age.
- Nevirapine tablets and nevirapine extended-release tablets are a type of HIV medicine called a non-nucleoside reverse transcriptase inhibitor (NNRTI).

Nevirapine extended-release tablets are not for use in children less than 6 years of age.

When used with other HIV medicines, nevirapine may:

1. Reduce the amount of HIV in your blood (called "viral load").
2. Help increase the number of CD4 (T) cells in your blood which help fight off other infections.

Reducing the amount of HIV and increasing the CD4 (T) cell count may improve your immune system. This may reduce your risk of death or infections that can happen when your immune system is weak (opportunistic infections).

Nevirapine does not cure HIV infection or AIDS.

Nevirapine does not cure HIV or AIDS and you may continue to experience illnesses associated with HIV-1 infection, including opportunistic infections. You should remain under the care of a doctor when using nevirapine.

You must stay on continuous HIV therapy to control HIV infection and decrease HIV-related illnesses.

Avoid doing things that can spread HIV-1 infection to others:

- **Do not share needles or other injection equipment.**
- **Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.**
- **Do not have any kind of sex without protection.** Always practice safe sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, or blood.

Ask your doctor if you have any questions on how to prevent passing HIV to other people.

Who should not take nevirapine?

Tell your doctor if you have or have had liver problems. Your doctor may tell you not to take nevirapine if you have certain liver problems.

Nevirapine is only for people diagnosed with HIV. If you have not been diagnosed as HIV positive, then do not take nevirapine.

What should I tell my doctor before taking nevirapine?

Before you take nevirapine, tell your doctor if you:

- have or have had hepatitis (inflammation of your liver) or problems with your liver. See **"What is the most important information I should know about nevirapine?"** and **"Who should not take nevirapine?"**
- receive dialysis
- have skin problems, such as a rash
- or your child has trouble swallowing pills
- have any other medical conditions
- are pregnant or plan to become pregnant. It is not known if nevirapine will harm your unborn baby.

Pregnancy Registry: There is a pregnancy registry for women who take antiviral medicines during pregnancy. The purpose of the registry is to collect information about the health of you and your baby. Talk to your doctor about how you can take part in this registry.

- are breastfeeding or plan to breastfeed. Nevirapine can pass into your breast milk and may harm your baby. You should not breastfeed if you have HIV because of the risk of passing HIV to your baby. Do not breastfeed during treatment with nevirapine. Talk to your doctor about the best way to feed your baby.

Tell your doctor and pharmacist about all the medicines you take, including prescription and over-the-counter medicines, vitamins and herbal supplements. Nevirapine may affect the way other medicines work, and other medicines may affect how nevirapine works.

You should not take nevirapine if you also take:

- St. John's wort. St. John's wort can lower the amount of nevirapine in your body.
- efavirenz (Sustiva®, Atripla®), etravirine (Intelence®), rilpivirine (Edurant®, Complera®), or delavirdine (Rescriptor®).
- boceprevir (Victrelis®)
- telaprevir (Incivek®)
- atazanavir (Reyataz®)
- lopinavir and ritonavir (Kaletra®) once daily
- fosamprenavir calcium (Lexiva®) without ritonavir (Norvir®)
- itraconazole (Sporanox®)
- ketoconazole (Nizoral®)
- rifampin (Rifadin®, Rifamate®, Rifater®)
- birth control pills. Birth control pills taken by mouth (oral contraceptives) and other hormone types of birth control may not work to prevent pregnancy. Talk with your doctor about other types of birth control that you can use to prevent pregnancy during treatment with nevirapine.

Also tell your doctor if you take:

- clarithromycin (Biaxin®)
- fluconazole (Diflucan®)
- indinavir sulfate (Crixivan®)
- methadone
- nelfinavir mesylate (Viracept®)
- rifabutin (Mycobutin®)
- warfarin (Coumadin®, Jantoven®)
- saquinavir mesylate (Invirase®)
- amiodarone, disopyramide (Norpace®), lidocaine
- carbamazepine, clonazepam (Klonopin®), ethosuximide (Zarontin®)
- diltiazem, nifedipine, verapamil
- cyclophosphamide
- ergotamine
- cyclosporine, tacrolimus, sirolimus (Rapamune®)
- cisapride (Propulsid®)
- fentanyl

If you are not sure if you take a medicine above, ask your doctor or pharmacist.

Know the medicines you take. Keep a list of them to show your doctor or pharmacist when you get a new medicine.

How should I take nevirapine?

- Nevirapine is always taken in combination with other anti-HIV medications.
- Nevirapine comes in three different forms. Your doctor will prescribe the form of nevirapine that is right for you.
  - o Nevirapine tablets
  - o Nevirapine oral suspension
  - o Nevirapine extended-release tablets
- Take nevirapine exactly as your doctor tells you to take it. Do not change your dose unless your doctor tells you to.
- You should never take more than one form of nevirapine at the same time. Talk to your doctor if you have any questions.
- If your child is prescribed nevirapine, your child's doctor will tell you exactly how nevirapine should be taken.
- Swallow nevirapine extended-release tablets whole. Do not chew, crush, or divide nevirapine extended-release tablets.
- You may take nevirapine with or without food.
- Do not miss a dose of nevirapine. If you miss a dose of nevirapine, take the missed dose as soon as you remember. If it is almost time for your next dose, do not take the missed dose, just take the next dose at your regular time. Do not take two doses at the same time.
- If you stop taking nevirapine for more than 7 days, ask your doctor how much to take before you start taking it again. You may need to begin taking the nevirapine starting dose again, which is taken one time each day for 14 days.

Starting nevirapine extended-release tablets when this is the first time you are taking any form of nevirapine:

1. Your doctor should start you with one dose of nevirapine tablets or oral suspension each day to lower your risk of getting a serious rash. **It is important that you only take one dose of nevirapine each day for the first 14 days.**
   - **Call your doctor right away if you get a skin rash during the first 14 days of nevirapine treatment.**
   - You should never take your starting dose for longer than 28 days. If after 28 days you are still receiving this starting dose because you have a rash, you and your doctor should talk about prescribing another HIV medicine for you instead of nevirapine.
   - **Do not start nevirapine extended-release tablets if you have a rash.**
2. Day 15, take nevirapine extended-release tablets one time a day as prescribed by your doctor.

Switching from nevirapine tablets or oral suspension to nevirapine extended-release tablets:

Take nevirapine extended-release tablets one time a day as prescribed by your doctor.

You may sometimes pass a soft mass in your stools (bowel movement) that looks like your nevirapine extended-release tablets. This will not affect the way your medicine works.

What are the possible side effects of nevirapine?

Nevirapine may cause serious side effects, including:

- See **"What is the most important information I should know about nevirapine?"**
- **Changes in your immune system (Immune Reconstitution Syndrome)** can happen when you start taking HIV medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time. Tell your doctor if you start having new symptoms after starting your HIV medicine.
- **Changes in body fat** can happen in some people who take antiretroviral therapy. These changes may include increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the middle of your body (trunk). Loss of fat from your legs, arms, and face can also happen. The cause and long-term health effects of these problems are not known at this time.

The most common side effect of nevirapine is rash.

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of nevirapine. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store nevirapine extended-release tablets?

- Store nevirapine extended-release tablets at room temperature between 20° to 25°C (68° to 77°F).
- Throw away nevirapine extended-release tablets that are no longer needed or out-of-date.

Keep nevirapine extended-release tablets and all medicines out of the reach of children.

General information about nevirapine extended-release tablets.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not take nevirapine for a condition for which it was not prescribed. Do not give nevirapine extended-release tablets to other people, even if they have the same condition you have. They may harm them.

This Medication Guide summarizes the most important information about nevirapine extended-release tablets. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about nevirapine extended-release tablets that is written for health professionals.

For more information, call Mylan Pharmaceuticals Inc. at
1-877-446-3679 (1-877-4-INFO-RX).

What are the ingredients in nevirapine extended-release tablets?

Active ingredient: nevirapine, USP

Inactive ingredients: hypromellose, lactose monohydrate and sodium stearyl fumarate

This Medication Guide has been approved by the U.S. Food and Drug Administration

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Mylan Pharmaceuticals Inc.
Mo ga ow WV 26505 U S A

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For current labeling information, please visit https://www.fda.gov/drugsatfda

MEDICATION GUIDE
NEVIRAPINE EXTENDED-RELEASE TABLETS
(ne vir′ a peen)
100 mg

Read this Medication Guide before you start taking nevirapine extended-release tablets and each time you get a refill. There may be new information. This information does not take the place of talking to your doctor about your medical condition or treatment.

What is the most important information I should know about nevirapine?

Nevirapine can cause serious side effects. These include severe liver and skin problems that can cause death. These problems can happen at any time during treatment, but your risk is higher during the first 18 weeks of treatment.

1. **Severe liver problems:** Anyone who takes nevirapine may get severe liver problems. In some cases these liver problems can lead to liver failure and the need for a liver transplant, or death.

   People who have a higher $CD4^+$ cell count when they begin nevirapine treatment have a higher risk of liver problems, especially:
   - Women with $CD4^+$ counts higher than 250 cells/mm^3. This group has the highest risk.
   - Men with $CD4^+$ counts higher than 400 cells/mm^3.

   If you are a woman with $CD4^+$ counts higher than 250 cells/mm^3 or a man with $CD4^+$ counts higher than 400 cells/mm^3, you and your doctor will decide whether starting nevirapine is right for you.

   In general, women have a higher risk of liver problems compared to men.

   People who have abnormal liver test results before starting nevirapine treatment and people with hepatitis B or C also have a greater risk of getting liver problems.

   You may get a rash if you have liver problems.

   Stop taking nevirapine and call your doctor right away if you have any of the following symptoms of liver problems:

   - dark (tea colored) urine
   - yellowing of your skin or whites of your eyes
   - light-colored bowel movements (stools)
   - fever
   - nausea (feeling sick to your stomach)
   - feel unwell or like you have the flu
   - pain or tenderness on your right side below your ribs
   - tiredness
   - loss of appetite

   Your doctor should see you and do blood tests often to check your liver function during the first 18 weeks of treatment with nevirapine. You should continue to have your liver checked regularly during your treatment with nevirapine. It is important for you to keep all of your doctor appointments.

2. **Severe rash and skin reactions:** Skin rash is the most common side effect of nevirapine. Most rashes happen in the first 6 weeks of taking nevirapine. **Rashes and skin reactions may be severe, life-threatening, and in some people, may lead to death. Stop using nevirapine and call your doctor right away if you get a rash with any of the following symptoms:**

   - blisters
   - mouth sores
   - red or inflamed eyes, like "pink eye" (conjunctivitis)
   - liver problems (see symptoms of liver problems above)
   - swelling of your face
   - fever
   - feel unwell or like you have the flu
   - tiredness
   - muscle or joint aches

If your doctor tells you to stop treatment with nevirapine because you have had any of the serious liver or skin problems described above, you should never take nevirapine again.

See the section **"What are the possible side effects of nevirapine?"** for more information.

What is nevirapine?

- Nevirapine tablets and nevirapine oral solution are prescription HIV medicines used with other HIV medicines to treat HIV (Human Immunodeficiency Virus). HIV is the virus that causes AIDS (Acquired Immune Deficiency Syndrome).
- Nevirapine extended-release tablets are a prescription medicine used with other HIV medicines to treat HIV (Human Immunodeficiency Virus) in adults and in children who are 6 years of age to less than 18 years of age.
- Nevirapine tablets and nevirapine extended-release tablets are a type of HIV medicine called a non-nucleoside reverse transcriptase inhibitor (NNRTI).

Nevirapine extended-release tablets are not for use in children less than 6 years of age.

When used with other HIV medicines, nevirapine may:

1. Reduce the amount of HIV in your blood (called "viral load").
2. Help increase the number of CD4 (T) cells in your blood which help fight off other infections.

Reducing the amount of HIV and increasing the CD4 (T) cell count may improve your immune system. This may reduce your risk of death or infections that can happen when your immune system is weak (opportunistic infections).

Nevirapine does not cure HIV infection or AIDS.

Nevirapine does not cure HIV or AIDS and you may continue to experience illnesses associated with HIV-1 infection, including opportunistic infections. You should remain under the care of a doctor when using nevirapine.

You must stay on continuous HIV therapy to control HIV infection and decrease HIV-related illnesses.

Avoid doing things that can spread HIV-1 infection to others:
- **Do not share needles or other injection equipment.**
- **Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.**
- **Do not have any kind of sex without protection.** Always practice safe sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, or blood.

Ask your doctor if you have any questions on how to prevent passing HIV to other people.

Who should not take nevirapine?

Tell your doctor if you have or have had liver problems. Your doctor may tell you not to take nevirapine if you have certain liver problems.

Nevirapine is only for people diagnosed with HIV. If you have not been diagnosed as HIV positive, then do not take nevirapine.

What should I tell my doctor before taking nevirapine?

Before you take nevirapine, tell your doctor if you:
- have or have had hepatitis (inflammation of your liver) or problems with your liver. See **"What is the most important information I should know about nevirapine?"** and **"Who should not take nevirapine?"**
- receive dialysis
- have skin problems, such as a rash
- or your child has trouble swallowing pills
- have any other medical conditions
- are pregnant or plan to become pregnant. It is not known if nevirapine will harm your unborn baby.

Pregnancy Registry: There is a pregnancy registry for women who take antiviral medicines during pregnancy. The purpose of the registry is to collect information about the health of you and your baby. Talk to your doctor about how you can take part in this registry.

- are breastfeeding or plan to breastfeed. Nevirapine can pass into your breast milk and may harm your baby. You should not breastfeed if you have HIV because of the risk of passing HIV to your baby. Do not breastfeed during treatment with nevirapine. Talk to your doctor about the best way to feed your baby.

Tell your doctor and pharmacist about all the medicines you take, including prescription and over-the-counter medicines, vitamins and herbal supplements. Nevirapine may affect the way other medicines work, and other medicines may affect how nevirapine works.

You should not take nevirapine if you also take:
- St. John's wort. St. John's wort can lower the amount of nevirapine in your body.
- efavirenz (Sustiva®, Atripla®) , etravirine (Intelence®), rilpivirine (Edurant®, Complera®), or delavirdine (Rescriptor®).
- boceprevir (Victrelis®)
- telaprevir (Incivek®)
- atazanavir (Reyataz®)
- lopinavir and ritonavir (Kaletra®) once daily
- fosamprenavir calcium (Lexiva®) without ritonavir (Norvir®)
- itraconazole (Sporanox®)
- ketoconazole (Nizoral®)
- rifampin (Rifadin®, Rifamate®, Rifater®)
- birth control pills. Birth control pills taken by mouth (oral contraceptives) and other hormone types of birth control may not work to prevent pregnancy. Talk with your doctor about other types of birth control that you can use to prevent pregnancy during treatment with nevirapine.

Also tell your doctor if you take:
- clarithromycin (Biaxin®)
- fluconazole (Diflucan®)
- indinavir sulfate (Crixivan®)
- methadone
- nelfinavir mesylate (Viracept®)
- rifabutin (Mycobutin®)
- warfarin (Coumadin®, Jantoven®)
- saquinavir mesylate (Invirase®)
- amiodarone, disopyramide (Norpace®), lidocaine
- carbamazepine, clonazepam (Klonopin®), ethosuximide (Zarontin®)
- diltiazem, nifedipine, verapamil
- cyclophosphamide
- ergotamine
- cyclosporine, tacrolimus, sirolimus (Rapamune®)
- cisapride (Propulsid®)
- fentanyl

If you are not sure if you take a medicine above, ask your doctor or pharmacist.

Know the medicines you take. Keep a list of them to show your doctor or pharmacist when you get a new medicine.

How should I take nevirapine?
- Nevirapine is always taken in combination with other anti-HIV medications.
- Nevirapine comes in three different forms. Your doctor will prescribe the form of nevirapine that is right for you.
  - o Nevirapine tablets
  - o Nevirapine oral suspension
  - o Nevirapine extended-release tablets
- Take nevirapine exactly as your doctor tells you to take it. Do not change your dose unless your doctor tells you to.
- You should never take more than one form of nevirapine at the same time. Talk to your doctor if you have any questions.
- If your child is prescribed nevirapine, your child's doctor will tell you exactly how nevirapine should be taken.
- Swallow nevirapine extended-release tablets whole. Do not chew, crush, or divide nevirapine extended-release tablets.
- You may take nevirapine with or without food.
- Do not miss a dose of nevirapine. If you miss a dose of nevirapine, take the missed dose as soon as you remember. If it is almost time for your next dose, do not take the missed dose, just take the next dose at your regular time. Do not take two doses at the same time.
- If you stop taking nevirapine for more than 7 days, ask your doctor how much to take before you start taking it again. You may need to begin taking the nevirapine starting dose again, which is taken one time each day for 14 days.

Starting nevirapine extended-release tablets when this is the first time you are taking any form of nevirapine:

1. Your doctor should start you with one dose of nevirapine tablets or oral suspension each day to lower your risk of getting a serious rash. **It is important that you only take one dose of nevirapine each day for the first 14 days.**
   - **Call your doctor right away if you get a skin rash during the first 14 days of nevirapine treatment.**
   - You should never take your starting dose for longer than 28 days. If after 28 days you are still receiving this starting dose because you have a rash, you and your doctor should talk about prescribing another HIV medicine for you instead of nevirapine.
   - **Do not start nevirapine extended-release tablets if you have a rash.**
2. Day 15, take nevirapine extended-release tablets one time a day as prescribed by your doctor.

Switching from nevirapine tablets or oral suspension to nevirapine extended-release tablets:

Take nevirapine extended-release tablets one time a day as prescribed by your doctor.

You may sometimes pass a soft mass in your stools (bowel movement) that looks like your nevirapine extended-release tablets. This will not affect the way your medicine works.

What are the possible side effects of nevirapine?

Nevirapine may cause serious side effects, including:
- See **"What is the most important information I should know about nevirapine?"**
- **Changes in your immune system (Immune Reconstitution Syndrome)** can happen when you start taking HIV medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time. Tell your doctor if you start having new symptoms after starting your HIV medicine.
- **Changes in body fat** can happen in some people who take antiretroviral therapy. These changes may include increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the middle of your body (trunk). Loss of fat from your legs, arms, and face can also happen. The cause and long-term health effects of these problems are not known at this time.

The most common side effect of nevirapine is rash.

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of nevirapine. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store nevirapine extended-release tablets?
- Store nevirapine extended-release tablets at room temperature between 20° to 25°C (68° to 77°F).
- Throw away nevirapine extended-release tablets that are no longer needed or out-of-date.

Keep nevirapine extended-release tablets and all medicines out of the reach of children.

General information about nevirapine extended-release tablets.
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not take nevirapine for a condition for which it was not prescribed. Do not give nevirapine extended-release tablets to other people, even if they have the same condition you have. They may harm them.

This Medication Guide summarizes the most important information about nevirapine extended-release tablets. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about nevirapine extended-release tablets that is written for health professionals.

For more information, call Mylan Pharmaceuticals Inc. at 1-877-446-3679 (1-877-4-INFO-RX).

What are the ingredients in nevirapine extended-release tablets?

Active ingredient: nevirapine, USP

Inactive ingredients: hypromellose, lactose monohydrate and sodium stearyl fumarate

This Medication Guide has been approved by the U.S. Food and Drug Administration

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Mylan®

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Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

Manufactured in India by:
Mylan Laboratories Limited
Hyderabad — 500 034, India

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